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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/506,011	02/17/2000	John Cooper Cox	017227/0155	6856

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EXAMINER
FOLEY, SHANON A

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 02/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/506,011	Applicant(s) COX ET AL.	
	Examiner Shanon A. Foley	Art Unit 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43 and 52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-43 and 52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Raw sequence error report* .

DETAILED ACTION

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-43 and 52 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-32 and 35-47 of copending Application No. 09/714438 for reasons of record.

Applicant states willingness to submit a terminal disclaimer once patentable subject matter is indicated.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-43 and 52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for peptides HpC, SYI, YPH, or RPQ with 6 lysines (K) and 6 histidines (H) associated with cardiolipin (CDL) or diphosphoryl lipid A (DPL), or CHL, does not reasonably provide enablement for any positively charged protein and any negatively

charged adjuvant to prevent, inhibit, halt, or delay the onset or progression of any microbial pathogen or cancer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for reasons of record.

Applicant states in the second paragraph under "PARAGRAPH 1" on page 4 of the response that the association of the negative charge on the organic complex was increased by the incorporation of DPL and is unrelated to whether or not there were additional lysines present.

The Office action was merely broadly summarizing the examples in the specification. It is noted that DPL was not incorporated into an existing negatively charged organic adjuvant that would increase an already existing association, but rather DPL was one of the adjuvants used to determine association capacity between adjuvant and antigens.

Applicant disagree that there is no indication that specific CTL responses in mice were directed against the antigen or the adjuvant and cites data generated in the instant examples that indicate that specific CTL responses were directed against antigen.

Applicant's arguments as well as a review of the data in the examples have been considered. However, it is maintained that a specific CTL response directed against the antigen has not been demonstrated. Example 4 on page 25 that applicant has referred to demonstrates that a CTL response was generated in response to EPO associated with ISCOMATRIX™, but there was no CTL response generated against EPO alone. Since there is no data provided for whether a CTL response is generated against the adjuvant alone, it cannot be determined whether the CTL response observed is directed against the adjuvant alone or the antigen associated with the adjuvant. Therefore, it is maintained that while the specification teaches that mice had a CTL

response in examples 4, 6, 9, 14, and 17, there is no indication that the response was directed to the antigen specifically or to the particular ISCOMATRIX™ used to boost the response to the antigen. Furthermore, the mice were never challenged with any pathogen directly after immunization to test for efficacy or to examine how long the antigen/adjuvant remained *in vivo*.

Applicant further asserts that there is no unpredictability with how well the proteins will associate on the grounds that the TYQ epitope induced a weak response in example 17 and a strong response in example 14.

In response to arguments directed to unpredictability, it is conceded that a CTL response, however weak, is still a CTL response. However, in view of the wide variation of responses observed with the same epitope when combined with different adjuvants, it is maintained that there is unpredictability between protein/adjuvant associations, which is consistent with the teachings of Barr et al.

Applicant states that Barr et al. describes difficulties the instant invention overcomes, which is directed toward obviating the need for introducing hydrophobic regions into antigens. In addition, applicant states that it is not clear how the teachings of Offringa et al. are relevant to the instant invention since the reference uses a completely different adjuvant from the instant adjuvant complex.

Applicant's arguments have been considered, but are unpersuasive because the claims do not recite non-hydrophobic regions in antigens. The invention is drawn to electromagnetic associations between antigens and adjuvants. Therefore, since the teachings of Barr et al. are pertinent with respect to antigen and adjuvant charges, i.e. hydrophobicity, and difficulties associated with antigen/ISCOM™ complexes, which are used in the instant examples and recited

in the claims, the teachings of Barr et al. offer relevant teachings in the ISCOM™ art. With respect to the teachings of Offringa et al., the reference is cited as a general teaching with respect to cancer therapy and the use of antigen/adjuvant complexes that would raise concerns of the skilled artisan with regard to the instant invention and cancer therapy.

Applicant argues that undue experimentation is not required to make or use the invention because the specification teaches a means for associating, increasing association, and testing the association between a charged organic complex and antigen to create an immunogenic complex that routinely induces a CTL response.

As stated in the previous Office action, the invention is enabled for antigen/adjuvant complexes, but is not reasonably enabled for any positively charged protein and any negatively charged adjuvant to prevent, inhibit, halt, or delay the onset or progression of any microbial pathogen or cancer for reasons of record.

Claim Rejections - 35 USC § 102

Claim Rejections - 35 USC § 103

Claims 1-8 and 12-14 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Nakanishi et al. for reasons of record.

Applicant argues that Nakanishi et al. teaches away from the instant invention because the reference teaches that only positively charged liposomes could induce a CTL response. Applicant also briefly summarizes a very detailed anatomy of phospholipids and how they are loaded.

The examiner appreciates the discussion of phospholipids applicant has provided. However, the arguments are not convincing because the claims Nakanishi et al. anticipates or

renders obvious are not directed to generating a CTL response. The claims are drawn to a negatively charged adjuvant and a positively charged antigen. Nakanishi et al. clearly anticipates the negatively charged phospholipid adjuvant, see "Negatively charged" under "Surface charge of liposome" in Table 1. The vesicles of Nakanishi et al. all contain phosphatidylcholine and have been enhanced to become more negatively charged by the addition of phophatidic acid. Therefore, even though Nakanishi et al. does not explicitly teach that the antigens have a positive charge and are electrostatically associated with the negatively charged vesicle, the reference does teach that the negatively charged vesicles are composed of phosphatidylcholine. The negatively charged end of this molecule would be found in the interior of the vesicle, which associates directly with the protein antigen. Since some amino acids inherently have a positive charge, and these amino acids would be naturally attracted to the negative charge of the phosphatidylcholine, creating an electrostatic association between the antigen and the vesicle in some degree. Therefore, the teachings of Nakanishi et al. render the invention obvious, if not anticipated.

Claims 9-11 and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nakanishi et al. as applied to claims 1-8, 12-14 above, and further in view of Barr et al. for reasons of record.

Applicant disagrees that the claims are rendered obvious by the combined teachings of Nakanishi et al. and Barr et al. Applicant states the differences between phospholipids and saponins structure and their immununogenic nature, and states that the two are not variants of one another. Applicant states that the art does not teach or suggest incorporating MPL or DPL or any other lipid to increase surface charge.

Again, the examiner appreciates applicant's teaching between phospholipids and saponins. However, the applicant's arguments are unconvincing in view of the prior art. Nakanishi et al. teaches negatively charged liposomes comprising phophatidic acid to enhance negative charge and antigen complex. Nakanishi et al. does not teach ISCOMATRIX™, lipid A. However, Barr et al., reviews organic adjuvants such as ISCOMATRIX™, lipid A, as well as phospholipids used by Nakanishi et al. and teaches that these complexes induce a wide range of CTL responses, see pages 14 (bottom) -15. Barr et al. also discusses the differences between the adjuvants discussed by applicant. Therefore, depending on the antigen's size and other considerations, such as ease of antigen loading, ect., the ordinary artisan would have been motivated substitute one of alternative organic adjuvants taught by Barr et al. in place of the negatively charged liposome of Nakanishi et al., rendering the invention prima facie obvious, absent unexpected results.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon A. Foley whose telephone number is (703) 308-3983. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (703) 308-4027. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4426 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Shanon Foley/SAF
February 11, 2002

ALI R. SALIMI
PRIMARY EXAMINER